

Tumor Lysis Syndrome

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RENAL FAILURE occurs as a complication of malignant disease in a variety of clinical situations and for a variety of reasons including direct (eg, tumor invasion) and/or indirect (eg, Bence-Jones protein deposition) effects of the tumor as well as the effects of therapy. The acute tumor lysis syndrome is perhaps the most dramatic cause of acute renal failure in cancer patients because it is often fulminant in onset, associated with malignant hyperkalemia, and usually completely reversible. It is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute, often oliguric renal failure. Typically patients with tumor lysis syndrome are critically ill from rapidly growing hematologic malignancies. Evidence of tumor lysis with renal failure is seen in up to two thirds of patients before treatment of any kind; furthermore, chemotherapy may accelerate or precipitate acute renal failure in this setting.¹ The pathophysiology of this syndrome is based on the fact that rapid cell turnover in aggressive malignancies renders these tumors susceptible to rapid, massive, cell death with or without cytoreductive treatment. Rapid cell lysis liberates metabolites that under normal circumstances are excreted without injury but are nephrotoxic in this setting. Although it is a serious complication, renal failure in most cases is reversible, and patients can be managed successfully with conservative and/or hemodialysis therapy. The purpose of this review is to update the reader on the pathogenesis, diagnosis, and treatment of this syndrome with an emphasis on the spectrum of presentation of renal failure and the importance of dialytic management.

HISTORY

Tumor lysis syndrome was recognized as a cause of renal failure before the advent of combination chemotherapy for solid and lymphoproliferative tumors. Tumor lysis following malignancy was originally described by Bedrna and Polcak in 1929 in patients with chronic leukemia.² Later Merrill called attention to the syndrome in patients with acute leukemia, hyperuricemia, and renal failure³; however, the nature of

the renal disease was not further elucidated until the early 1960s when the association of hyperuricemia with renal failure began to appear in the literature.⁴⁻⁶ Renal tissue of patients with this syndrome disclosed that tubular lumina were obstructed by abundant uric acid crystals. Krakoff and Meyer⁵ as well as other investigators demonstrated that patients with massive, aggressive, lymphoproliferative malignancies undergoing chemotherapy, pretreatment with allopurinol could prevent or attenuate hyperuricemia and renal failure. Further reports indicated that this was a reproducible effect of allopurinol, and by the early 1970s allopurinol was routinely used as prophylaxis for all patients undergoing chemotherapeutic agents in the setting of rapidly proliferating tumors. Unfortunately, not all patients prophylaxed with allopurinol were spared from nephrotoxicity, and soon hyperphosphatemia with interstitial deposition of calcium-phosphate complexes were implicated in renal failure observed after chemotherapy with allopurinol prophylaxis.^{1,7} It is now recognized that the renal failure in tumor lysis syndrome is indeed multifactorial and can be caused by calcium-phosphate as well as uric acid deposition in the kidney.

CLINICAL SETTING

General

Tumor lysis syndrome develops during the rapid growth phase of malignancies such as bulky lymphoblastomas and Burkitt and nonBurkitt aggressive lymphomas that are known to have extraordinarily rapid cell turnover rates.^{7a} The combination of massive tumor bulk, rapid cell turnover, and exquisite sensitivity to cytoreductive treatment renders these patients susceptible to rapid tumor lysis, which in turn sets into motion the events leading to renal failure. However,

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0270-9295/93/1303-0002\$5.00/0*

renal failure from tumor lysis has been reported in other hematologic as well as nonhematologic malignancies with a variety of cytoreductive therapies including leukemias, lung and breast cancer,⁸⁻¹⁷ and in bone-marrow transplantation.¹⁸ Moreover, it has been increasingly recognized in patients treated with high doses of glucocorticoids without concomitant chemotherapy.¹⁹⁻²² Taken together these reports suggest that the most important factor in the pathogenesis of this syndrome is rapid cell lysis that overwhelms normal renal excretory and cellular buffering mechanisms leading to elevation of the serum concentration of nuclear metabolites and acute renal failure. This sequence of events is accelerated by chemotherapy but most often occurs independent of it. Importantly, in most patients renal failure is completely reversible when prompt and aggressive supportive care including hemodialysis is administered.

Clinical Profile and Predisposing Factors

Susceptible patients tend to be young, often less than 25 years of age, male, and have an advanced disease stage, with abdominal disease present in association with high serum lactate dehydrogenase (LDH) levels¹ (Table 1). In addition, preexisting volume depletion, an acid-concentrated urine, and excessive urinary uric acid excretion rates may be important predisposing factors in many, if not all, patients.^{6,23} Azotemia in association with hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia is generally present before chemotherapy and is aggravated within 48 to 72 hours after treatment is instituted. In many of these cases hyperuricemia develops despite allopurinol prophylaxis; moreover, prevention of hyperuricemia does not necessarily prevent renal failure (see below).²⁴⁻²⁶ Thus although allopurinol decreases the magnitude of hyperuricemia, it does not necessarily prevent an acute increase in serum uric acid level.

PATHOPHYSIOLOGY OF RENAL FAILURE

The pathophysiology of renal failure in the acute tumor lysis syndrome is not completely understood; however, two major pathogenetic factors are important based on clinical findings in the majority of the reported cases. First, it is well appreciated that varying degrees of preex-

Table 1. Clinical Profile of Typical Patient at Risk for Tumor Lysis Syndrome

Young (often <25)
Male
Lymphoproliferative malignancy with abdominal involvement
Markedly elevated serum LDH
Presence of volume depletion
Concentrated, acid urine pH

isting volume depletion are present before the onset of renal failure in many, if not all, patients. Second, precipitation of uric acid and/or calcium phosphate complexes in the renal tissue causing acute renal injury plays a major role. Clinical and experimental evidence supports a role for both these factors.^{4,5,27-29}

Role of Volume Depletion

The importance of volume depletion has been repeatedly emphasized in the literature. Most authors³⁰ report that volume expansion with induced-diuresis in both the clinical setting and experimental models can prevent or ameliorate acute renal failure caused by uric acid deposition.^{28,29,31} Volume depletion in patients with these malignancies occurs for several reasons: (1) Patients may be anorectic with poor oral fluid intake or may have gastrointestinal symptoms including nausea, vomiting, and diarrhea. (2) Fever and tachypnea leading to insensible losses may occur. (3) Staging work-up may include procedures for which the patient is unable to ingest food or water and/or receives intravenous radiocontrast. Thus it has been emphasized that establishing diuresis with a hypotonic urine is an important prophylactic and therapeutic maneuver in patients at risk of or afflicted by renal failure attributable to acute tumor lysis.

Role of Tumor Lysis Products

Uric acid. As pointed out above many of these patients have preexisting hyperuricemia before treatment with chemotherapeutic agents, and/or they develop some degree of hyperuricemia after therapy despite allopurinol prophylaxis.³⁰ Although this presentation is common, patients may present with tumor necrosis, hyperuricemia, and renal failure before the onset of therapy.^{1,4,30}

Uric acid is the end product of purine metabolism in humans. It has a pKa of 5.4 and is nearly completely ionized at physiological pH. However, in the renal tubule and in particular in the collecting ducts where luminal pH approaches 5.0, uric acid progressively becomes less ionized and in turn becomes less soluble. Furthermore, it is in these nephron segments that luminal concentration increases because of urinary concentrating mechanisms. Indeed, histopathologic studies in humans and experimental animals with acute uric acid nephropathy indicate that intranephronal hydronephrosis is associated with uric acid precipitates which predominate in the distal nephron and in the medullary rays in particular.^{28,29,32} Moreover, a granulomatous reaction to intraluminal uric acid crystals as well as necrosis of distal tubular epithelium is present, with sparing of the proximal tubule being a notable feature.³² Finally, uric acid stones with ureteral and pelvic obstruction can occur as a result of tumor lysis leading to extranephronal urinary tract obstruction and acute renal failure. Conger et al²⁹ have shown that acute intravenous infusion of uric acid in rats sufficient to increase serum uric acid to levels comparable with those observed in humans with uric acid nephropathy is associated with deposition of uric acid in the distal tubules and medullary microcirculation that causes a sharp drop in glomerular filtration rate (GFR) and increases in intratubular pressure and renal vascular resistance. Further experiments in this model indicate that volume expansion and NaHCO₃ diuresis significantly attenuates but does not abolish the reduction in GFR. These data indicate that uric acid deposition causing intratubular obstruction is a major pathogenetic factor in the renal lesion of tumor lysis syndrome. They also suggest that a hemodynamic component is at least in part responsible for the decrease in GFR in rats.

Phosphate. In addition to renal uric acid crystallization, profound hyperphosphatemia and hypocalcemia occur commonly. In fact, acute renal failure attributable to metastatic intrarenal calcification or acute nephrocalcinosis has been reported in patients with rapid, massive, tumor lysis who develop posttreatment azotemia despite allopurinol therapy.^{1,33-35} In these cases uric acid nephropathy is not observed in renal tissue spec-

imens. The mechanism of hyperphosphatemia is the same as that of hyperuricemia, namely tumor lysis with release of inorganic phosphate from intracellular stores. Similar consequences have been observed in patients who received large oral, intravenous, or rectally administered exogenous phosphate loads.³⁶⁻³⁸ The net effect of sudden hyperphosphatemia is acute hypocalcemia and metastatic calcification causing acute renal failure.

Taken together, the evidence suggests that renal failure in tumor lysis syndrome results from a combination of volume depletion, hyperuricemia with acute uric acid precipitation in the renal tubule, the parenchyma (and occasionally the collecting system) and in some cases from acute nephrocalcinosis caused by severe hyperphosphatemia. Finally, it should be noted that urinary tract obstruction caused by extrinsic compression from massive retroperitoneal adenopathy may also contribute to renal failure in these patients.

DIAGNOSIS AND MANAGEMENT

Case Study

A 42-year-old black man with a history of intravenous drug abuse, alcohol abuse, and human immunodeficiency virus (HIV) infection was admitted to Parkland Memorial Hospital for rapidly accumulating ascites. The patient was known to be HIV positive since January 1992 but had no history of opportunistic infection. He was otherwise well until July 1992 when he noted a rapid increase in abdominal girth, pedal edema, and drenching night sweats. Over the next month he noted early satiety, boring abdominal pain, scleral icterus, and dark urine. Physical examination showed a febrile cachectic, icteric man with a massively enlarged abdomen with a prominent fluid wave as well as bipedal edema.

Admission laboratory tests showed serum Na 141, K 4.5, Cl 102, CO₂ 24, Cr 1.2, blood urea nitrogen (BUN) 9. The aspartate aminotransferase (AST) was 118, alanine aminotransferase (ALT) 50, gamma-glutamyltransferase (GGT) 4,004, alkaline phosphatase 437, total protein 8.4, albumin 3.4. The serum LDH 4,640 and CD4 count 165. Urinalysis was remarkable for 1 to 3 white blood cell count (WBC) high power field

(HPF) and 10 to 20 hyaline casts/HPF. A sonogram showed ascites, a dilated common bile duct, a large mass in the right lobe of the liver, and pericaval and periaortic adenopathy. The left kidney was 13 centimeters, the right kidney 15 centimeters, and mild bilateral hydronephrosis was noted. Paracentesis showed turbid, bloody fluid containing 22,000 white blood cells, many of which were atypical degenerating white cells. Cytological evaluation of the fluid showed a large cell lymphoma which was marked with B-cell markers. An abdominal computed tomographic (CT) scan on hospital day 9 showed an extrinsic mass compressing the right lobe of the liver as well as massive periaortic and pericaval adenopathy compressing the vena cava. A diagnosis of widespread B-cell large-cell lymphoma was made. The clinical course was judged to be as aggressive as Burkitt's lymphoma, which can be complicated by pancreatic and biliary obstruction. On the 9th hospital day, and before the CT scan, the patient's serum creatinine increased to 1.6. Over the next 7 days his serum potassium level increased to 5.5, phosphorus 5.1, Ca 9.6, and serum uric acid level was 14.8 mg/dL (Fig 1). On hospital day 18 he was administered intravenous fluids consisting of 0.45 NaHCO₃ at a rate of 200 mL/h. However, his creatinine, potassium, and phosphorus levels continued to increase over the next 24 hours. As a result hemodialysis was initiated and he was started on chemotherapy with cytoxan, vincristine, prednisone, and allopurinol. Despite dialysis the patient continued to exhibit increased serum potassium to 5.3 necessitating additional therapy with kayexalate. Despite allopurinol therapy, renal function deteriorated: phosphorus and uric acid levels increased and persisted. Dialysis and chemotherapy were continued. The patient remained nonoliguric during this time. On hospital day 21 he developed an acute upper gastrointestinal hemorrhage due to a severe gastric ulcer. This was managed with conservative therapy, and over the next 48 hours renal function began to improve. As renal function improved, serum calcium, phosphorus, potassium, and uric acid levels returned to normal. Over the next 10 days renal function improved further, with a new baseline creatinine of 0.9 mg/d and uric acid level decreased to 2.9 mg/d on allopurinol.

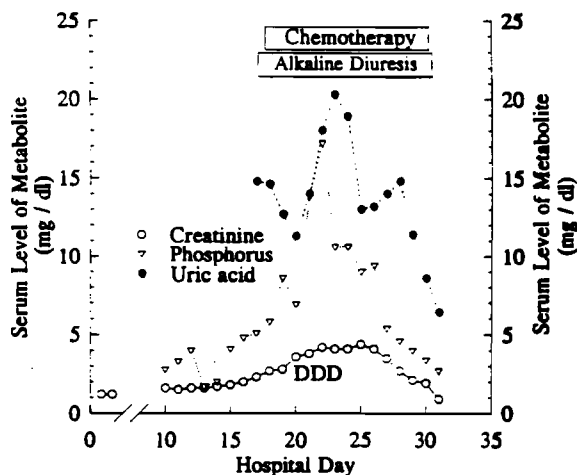


Fig 1. Serum creatinine, phosphorus, and uric acid level in a patient with tumor lysis syndrome. Renal function on admission was normal with serum creatinine of 1.2 mg/dL. On hospital day 9 serum creatinine was noted to be elevated to 1.6 mg/dL. Subsequently, on day 18, the patient was noted to have hyperuricemia and hyperphosphatemia. Despite alkaline diuresis and allopurinol therapy renal failure worsened necessitating dialysis. Upon institution of chemotherapy, hyperuricemia and hyperphosphatemia worsened and renal function deteriorated further. With continued supportive care, including hemodialysis and alkaline diuresis renal function, serum phosphorus and uric acid levels returned to normal.

This case illustrates several important features of the tumor lysis syndrome. First this patient was relatively young and had a very aggressive tumor with massive abdominal disease and striking elevation of serum LDH. Second, he developed renal failure before chemotherapy in the hospital during the work-up of his disease. Third, despite vigorous intravenous hydration, he rapidly developed hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia necessitating hemodialysis; moreover, hyperuricemia transiently worsened shortly after initiation of chemotherapy despite allopurinol prophylaxis. Fourth, with supportive therapy including hemodialysis renal function recovered completely. In addition, it is noteworthy that this patient had an element of hydronephrosis attributable to tumor compression of the ureters. This condition has been observed frequently in patients with aggressive abdominal disease.¹

Diagnosis

Any patient with a known or suspected malignancy, especially lymphomas of the Burkitt's

type, who presents with hyperuricemia, renal failure, and elevated serum LDH, should be examined for tumor lysis syndrome. The presence of concomitant volume depletion, hyperkalemia, hyperphosphatemia, and hypocalcemia strongly support this clinical diagnosis. The constellation of these findings is useful in differentiating tumor lysis syndrome from other causes of renal failure in cancer patients such as urinary tract obstruction, parenchymal infiltration with tumor, glomerulonephritis (eg, secondary to cryoglobulinemia or tumor-related antigen-antibody complexes), hypercalcemia, volume depletion, vasculitis, hypercalcemic nephropathy, myeloma kidney and drug nephrotoxicities (Table 2).

Management

Patients with tumor lysis syndrome are critically ill. They often are febrile, malnourished, susceptible to (and often empirically treated for) serious opportunistic infections, and subject to life-threatening metabolic and nutritional disturbances. Coordinated care in an intensive care unit using a team approach including nursing staff, the primary care physician, nephrologist, and oncologist is essential to successful management.

Management of renal failure can essentially be divided into two categories: (1) prevention/conservative management; and (2) dialysis therapy.

Prevention and conservative management. When the diagnosis of tumor lysis syndrome is suspected, preventive measures, including administration of allopurinol and intravenous fluid, should be undertaken. Because normal baseline serum creatinine often is not known and because most patients present with hyperuricemia in this setting, it is difficult to determine the onset of renal dysfunction. Therefore, in most instances, preventive measures and conservative management of renal failure are in fact one and the same. If a patient has hyperkalemia and hyperphosphatemia, it is likely that renal function is already impaired, even if serum creatinine is in the normal range. Therefore, prevention and conservative management are discussed together.

Allopurinol in doses of 600 mg/d should be given to decrease uric acid production. The patient should be administered intravenous fluid consisting of isotonic NaHCO_3 at a rate of 200

Table 2. Causes of Renal Failure in Cancer Patients

Urinary obstruction
Severe volume depletion
Parenchymal disease
Glomerulonephritis (eg, cryoglobulinemia)
Vasculitis
Hypercalcemic nephropathy
Tumor replacement
Tumor lysis syndrome
Acute uric acid nephropathy
Calcium/phosphate nephropathy
Myeloma kidney (cast nephropathy)
Drug nephrotoxicity
Methotrexate
Cis-platinum
Mitomycin C
Interferon- α
Interleukin 2
Antibiotics

to 300 mL/h for three reasons: (1) to expand volume, thereby diluting extracellular fluid and reducing serum concentrations of uric acid, phosphorus, and potassium; (2) to wash out the renal medulla, thereby decreasing the concentration of solutes in the distal nephron and medullary microcirculation; and (3) to alkalinize the urine, thereby solubilizing and thus minimizing intratubular precipitation of uric acid. Both maneuvers reduce the likelihood that oliguric renal failure will develop. Urine output and urine pH should be monitored closely to guide therapy. It is preferable to decrease urine osmolality to isotonic or hypotonic levels and to increase urine pH to 7.0. Both parameters can be monitored at the bedside. Urine osmolality can be estimated from the specific gravity in glucose-, mannitol-, and protein-free urine by multiplying the digits to the right of the decimal point in the specific gravity (SG) by 35 (eg, for SG = 1.010, Urine osm = $35 \times 10 = 350$ mosm/kg). Urine pH can be monitored at the bedside using a dipstick. Alkaline diuresis and allopurinol should be continued throughout the course of induction chemotherapy and for at least 2 to 3 days after the final dose of cytoreductive therapy.

Because of the rapid and unpredictable rate of tumor lysis, in these critically ill patients extreme and even fatal hyperkalemia have been reported³⁹⁻⁴¹; therefore, hyperkalemia should be vigorously and aggressively treated with measures aimed at removing potassium from the

body. It should be emphasized that maneuvers designed to shift potassium into cells to lower serum potassium are of limited value and should never be used as sole therapy in this circumstance; rather, immediate use of dietary K restriction, removal of potassium from intravenous infusates, administration of 50 to 100 grams of kayexalate as a retention enema, and prompt therapy with hemodialysis (see below) should be undertaken.

Deviations of serum calcium and phosphorus concentrations in blood generally occur together with onset of the syndrome, owing to phosphorus release. The time course of these alterations varies but usually lasts for 1 to 2 weeks. In most cases calcium returns to baseline along with phosphate. In some patients hypocalcemia may persist because of depressed serum $1,25\text{-(OH)}_2$ dihydroxycholecalciferol levels. In this circumstance exogenous administration of calcitriol may correct hypocalcemia.⁴² However, this should not be undertaken until serum phosphorus has returned to normal level and is stable.

Hemodialysis. Hemodialysis often is necessary and life-saving in the management of tumor lysis and should be considered for every patient. The main indications for dialysis is to reduce the load of metabolic toxins in the circulation, namely uric acid, phosphorus, and potassium, to control volume and to manage uremia. Virtually all patients with tumor lysis have one or more of these complications. Hemodialysis is preferred over peritoneal dialysis because of the markedly higher uric acid and phosphorus clearance rates achievable with this technique. The goals of dialysis therapy are to decrease plasma levels of uric acid, phosphorus, and potassium and to restore normal nitrogen balance (Table 3). Timing of initiation of dialysis should be determined on clinical grounds keeping in mind the fact that the catabolic rate is sharply increased in patients undergoing tumor lysis. For this reason daily hemodialysis generally is required, particularly during chemotherapy induction when the risk of developing tumor lysis is heightened. Whether dialysis should be used prophylactically has not yet been established; however, it was reported to be of benefit in a recent study using continuous atrioventric-

Table 3. Indications for Dialysis in the Tumor Lysis Syndrome

Hyperkalemia
Volume overload
Hyperphosphatemia
Control of uremia
Hypocalcemia
Hyperuricemia

ular (AV) hemofiltration (CAVH) to treat a child with undifferentiated lymphoblastic lymphoma.⁴³ In this study, after initiating a sodium bicarbonate diuresis, CAVH was instituted immediately before induction chemotherapy. This prevented hyperuricemia, hyperphosphatemia, and renal failure. In patients with established renal failure and hyperkalemia, it is advisable to initiate hemodialysis in conjunction with preventive/ameliorative therapy.

Monitoring. Daily weights, hourly intake and output, and serum electrolytes including potassium, calcium, phosphorus, and uric acid, should be performed at least twice daily and more frequently as needed if standard hemodialysis or CAVH/CAVHD are used.

Complications of therapy. Several complications of therapy have been reported in tumor lysis syndrome. Allopurinol is known to cause a rash that can be localized or systemic and mild or severe (eg, Stevens-Johnson syndrome). Furthermore, because it increases xanthine levels, urolithiasis due to xanthine stones may occur.⁴⁴ In addition, allopurinol rarely causes reversible renal failure due to acute interstitial nephritis.⁴⁵ Pneumopathy characterized by cough, tachypnea, severe hypoxemia, and extensive interstitial and alveolar infiltrates occurring within 24 to 72 hours of induction therapy has been reported recently.⁴⁶ Pulmonary edema has been reported during fluid administration during alkaline diuresis.³¹

SUMMARY

Tumor lysis syndrome is a critical illness characterized by massive tumor cell death leading to severe hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and acute renal failure in patients with rapidly growing cancers (especially Burkitt's lymphomas with extensive abdominal bulk). It may be prevent-

able with allopurinol therapy combined with aggressive intravenous fluid therapy aimed at establishing an ongoing alkaline diuresis. In most cases renal failure is completely reversible; however, fatal hyperkalemia and volume overload may develop. Therefore, aggressive management with hemodialysis often is necessary to

maintain life support while tumor burden is controlled with cytoreductive therapy. Early recognition and management by a team approach in the intensive care unit where careful monitoring is available serves to forestall severe renal failure, thereby improving short-term prognosis in susceptible patients.

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